Final Action Cover Sheet
Bristol-Myers Squibb Position Paper
Comments on Regulatory Actions

Name of Regulation/Guidance: Draft Guidance for Industry on Bioanalytical Methods Validation for Human Studies	
Type of Submission:	
To PhRMA [ ]	PhRMA Comment Due Date:
To FDA [X]	FDA Comment Due Date: March 8, 1999
Overview/Summary: The FDA has invited comments on a draft guidance for industry. B-MS has provided extensive comments and recommendations to these proposed guidelines.	
Request:	
Return to: Dr. M. L. Powell	Return By (date): 2/18/99
Approved By: Dr. R. H. Barbhaiya	Not Approved By:
Date Approved:	Date Rejected:
If not approved, please explain:	
Other Comments:	
SENT TO: Dr. L. Smaldone c/o L. Csillan	CC: J. Kenney Dr. L. Klunk (WFD)

98D-1195

C34

March 2, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

Re: Docket No. 98D-1195; Notice/Draft Guidance for Industry on Bioanalytical Methods Validation for Human Studies (*Federal Register, Vol. 64, No. 2, January 5, 1999)*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on this FDA proposal to provide assistance in developing validation information for bioanalytical methods used in human clinical pharmacology, bioavailability and bioequivalence studies for use in IND's, NDA's, ANDA's, and supplements.

General Comment

It is unclear why FDA would release these DRAFT guidelines at this time for comment. The pharmaceutical industry has been operating under the previous guidelines for approximately 9 years. It is our understanding that a joint AAPS/FDA follow up symposium is planned for later this year. The purpose of this symposium would be to revise and update the previous guidelines for bioanalytical method validations. We strongly recommend that these DRAFT guidelines not be finalized before this meeting.

Specific Comments

I. INTRODUCTION

It is not clear why the DRAFT guidelines should not also apply to nonhuman pharmacology/toxicology studies since the underlying principles are the same. We would recommend broadening them accordingly.

We have significant concerns that Immunochemistry based assays are included together with GC and HPLC assays. There are too many differences to easily categorize these methodologies together under one general set of guidelines. Accordingly, we would recommend that Immunochemistry guidelines be issued as a separate document.

Mass spectrometry (MS) based assays are not mentioned in the guidelines (e.g. LC-MS, LC-MS/MS or GC/MS) unless it should be inferred that MS is being treated as a GC or HPLC detector only. If this is the case, it must be clearly stated. In point of fact, more than 80% of our quantitative human bioanalytical methods are developed using LC-MS/MS and we are not unusual in the industry.

This guidance should NOT apply to analyses of tissue samples. This matrix is considerably different, and in many cases the requirements can not completely be met for a tissue assay.

II. BACKGROUND

Paragraph II Suggest deleting the term "reproducibility" here since it is not discussed in any subsequent sections of the document.

What is implied by the term "linearity"? It is unclear whether quadratic fits of data are excluded, which are integral to our general assay development activities. A better phrase is "predictive mathematical function" which will cover any type of curve fit. This general comment should be applied throughout the DRAFT document.

Paragraph III It is unclear what change of "instrument" and "detectors" means with regards to "full" versus "partial" revalidation. We would strongly object to the concept that changing manufacturer(s) of an identical type of instrument should require "full" revalidation of an assay.

Paragraph IV What does the term "closely adhere to" mean? Does this mean follow GLPs and/or could a company expect to be given a 483 if they didn't meet one or more of the specific aspects of these guidelines?

III. REFERENCE STANDARD

Replace the word "sample" in line 2 with the term "blank matrix" which is appropriately descriptive.

The description and purpose of the "**master standard**" are unclear. We have considered three possible interpretations:

1. The purity of any subsequent reference standard is to be assigned based on an HPLC assay of the new standard vs. the **master standard**. We do not agree with this interpretation since the precision of HPLC assays is typically no better than about ±0.5%, which we do not consider precise enough for assigning a purity value to a reference standard.

2. Any new reference standard should be assayed vs. the **master standard,** and the assay value should not be significantly different (e.g. at the 95% confidence level) from the assigned purity (however determined) of the new standard. This is questionably acceptable, since there is no way of completely ensuring that the **master standard** will not change over time.

3. The HPLC impurity profile of any new reference standard should be compared with that of the **master standard,** to determine the identities of impurities and to determine the presence and levels of any new and possibly interfering impurities, or impurities that may have unknown or different response factors when quantitated as an area percent. This interpretation is appropriate and acceptable, but additional clarification is highly desirable.

For biologicals, a **master standard** is rarely available.

IV. PRE-STUDY VALIDATION

Performance factors should not include "4) quality control samples". It isn't clear what the authors mean here.

As previous, the use of the term "linearity" should be replaced by "predictive mathematical function" which covers many types of curve fits.

We are opposed to the concept that every different matrix from every species requires "full validation". A less stringent "cross-validation" should be sufficient, for example, in mouse plasma if a fully validated assay in rat plasma has already been done. This could include LOQ, stability and one accuracy and precision run, for example.

A. Specificity

Paragraph I We are opposed to the concept requiring matrices to be obtained from individuals which includes "references to time of day, food ingestion, and other factors for an intended study". Often matrices are obtained from commercial sources that do not provide this information. Is there any data to suggest that these factors affect specificity in a significant way?

Typical pre-study validation is done well in advance of the majority of the anticipated clinical research program. Normal volunteer matrices are appropriate for pre-study validation.

Paragraph II The recommendation for exploring interferences is too restrictive because "significant" is not defined. Any significant interference that was present would, in any event, severely limit the scientist's ability to achieve low level quantitation. This specific section is not necessary.

Paragraph III It is excessive to require routine evaluation of OTC drugs and metabolites as potential interfering substances. LC-MS assays provide a level of selectivity as do Immunochemistry based assays, which eliminates this potential concern. It is appropriate to check anticipated co-meds which are either identified in a protocol or common to a patient population. Predose samples can be easily used for HPLC based assays to verify selectivity.

B. Calibration Curve

Although not clarified by the authors, we feel strongly that the calibration curve should consist of five to eight non-zero concentrations (each in duplicate) or minimally 10 to 12 discreet individual concentrations, along with a zero sample.

2. Linearity

This section does not adequately cover the inclusion of curve fitting for Immunochemistry based assays. If these types of assays remain part of this guidance, then this section needs to be expanded appropriately.

We question the value of using correlation coefficient (r) as a determining factor of the goodness of fit and recommend coefficient of determination as a more appropriate alternative.

C. Precision, Accuracy, and Recovery

The accuracy of a method is currently proposed as the "mean" value being within 15% of the actual value. We feel that individual values should be within 15% of the target value (20% at the LOQ).

It isn't clear if the recovery reference to results being "...as low as 50 to 60%" implies that values below 50% are not acceptable. We would argue that while not desirable, values below 50% might be acceptable if they were reproducible, accurate and precise.

D. Quality Control Samples

We are opposed to the use of 3 different batches of biological matrix for the validation runs where each batch is collected from a different source. If the purpose of validation is to mimic our approach to study sample analyses, we typically prepare enough QC samples from one batch of biological matrix to cover an entire study. We have already evaluated 6 different lots of biological matrix, so this is excessive and adds little additional value.

Since the LOQ is defined as the lowest point on the standard curve (Section B. Calibration Curve), it is not clear what value including a QC sample at the LOQ in each validation run adds. A one-time assessment of accuracy, precision, and specificity at the LOQ should be sufficient to define it.

E. Stability

1. Freeze and Thaw Stability

Suggest removing the term "unassisted" from the description. Thawing samples in warm water, for example, should be allowed. Particularly if this is how study samples will routinely be treated.

It is not clear why –20°C and –70°C were chosen as the two specific temperatures to do freeze thaw experiments at. We recommend that flexibility should be allowed for the laboratory to select what temperatures these experiments should be done at and define them as such in their method documentation.

F. Acceptance Criteria

In actual practice, will there be any flexibility for a laboratory to define a validated assay with wider acceptance criteria? This could be desirable, particularly for difficult assays. If so, this should be clearly stated in the guidelines.

V. IN-STUDY VALIDATION

Paragraph II The wording "...extrapolation of standard curves below LOQ or above the highest standard is not recommended" must be strengthened to read "...extrapolation of standard curves below LOQ or above the highest standard is not allowed."

VI. DOCUMENTATION

Paragraph III The description of data being recorded in a "bound laboratory notebook" should be made more general. Ring binders are commonly used at present along with bound notebooks, and the industry is now considering moving towards electronic notebooks.

We strongly object to the request for complete serial chromatograms from 20% of subjects to be submitted with a report. This imposes a significant additional burden on the laboratories, which adds little value. Actual chromatograms should be made available only upon request from the agency.

The final bullet requires clarification. What is meant by raw data and SOPs? Does raw data refer to instrument response values? Does the term SOP, as it is used here, refer to assay validation reports?

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

L. Smaldone

Laurie F. Smaldone
Senior Vice President
Worldwide Regulatory Affairs